REMARKS

The Official Action of June 15, 2004 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claims 2-11 have been canceled to remove the basis for the Examiner's claim objections on page 2 of the Official Action. Claims 20, 22 and 23 have been amended, and new claims 36-45 have been added more completely to define the subject matter which Applicants regard as their invention. The amendments to the claims and the recitations in the new claims draw clear support from the specification as filed at, for example, page 14, lines 7-10.

Claims 2-11, 20 and 22-30 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The rejection would appear to be based upon the contention that it would require undue experimentation for one of skill in the art to establish an amount of OPV effective to elicit a protective immune response against Type 1 diabetes mellitus (IDDM). Nevertheless, it is well-settled that, if one skilled in the art, based on knowledge of the same or similar compounds, would be able to discern an appropriate dosage of the claimed compound, this would be sufficient to satisfy the enablement provisions of 35 USC 112, first paragraph (see MPEP Section 2164.01(c)).

In the present case, the specification describes at page 9 that the claimed OPV dose can correspond to that which is used in the traditional Sabin-type OPV. In the paragraph bridging pages 14 and 15 of the specification, Applicants describe a study where this dose has been used on a whole population, and Fig. 1 illustrates the effectiveness of the vaccine in this dose on the prevalence of IDDM in the population. Since one of skill in the art clearly has knowledge of the dosage requirements for the recited vaccine based on the disclosure in the specification of the equivalence of the claimed dosage with dosages previously administered by those of skill in the art, it is respectfully submitted that one of skill in the art could determine the recited dosage without undue experimentation. Moreover, Applicants respectfully note that the specification also describes that repeated doses of OPV are preferred and provides a best mode vaccine regime in Table 1 on page 11 of the specification.

Insofar as the Examiner relies for support in the enablement rejection on publications which purport to reflect disagreement on the effect of OPV on enterovirus infection, Applicants respectfully submit that the publications are not competent even to meet the initial burden of the USPTO to cast doubt on the accuracy of Applicants' presumptively accurate disclosure (see MPEP Section 2164.04). These publications are discussed next.

The Office Action refers to an article by **Graves et al.,** which refers to a case-control study to determine whether early childhood immunization history affects the risk of developing the beta-cell autoimmunity that precedes type 1 diabetes. The

study includes four vaccines: HBV, Hib, polio (OPV) and DTP, and the authors found that there was no difference between cases and control subjects in the proportion receiving HBV, Hib, polio or DTP vaccines; in the proportion receiving HBV at birth rather than later; or in the median ages at first HBV, Hib, polio or DTP vaccination (see page 1; "Results"). Still the study focuses on the effect of HBV, and Hib, where there was a significant difference in the vaccination regime within the tested cohort. In the middle of page 4 the authors write: "All of the cases and >99% of the control subjects had received at least one polio and DTP immunization by 9 months of age. All polio vaccines were administered orally, and there was no difference in the median number of doses or the median age at first dose (Table 1)." Accordingly, since in practice all the children (that is both those developing type 1 diabetes and those of the control group) had received the same polio immunization, no conclusion can be drawn as to the influence of the polio vaccine on the outbreak of type 1 diabetes.

The **Graves et al.** article is based on a study of 317 children having a first-degree relative with type 1 diabetes. The number of cases with beta-cell autoimmunity was 25, and the number of control subjects (= the remainder of the cohort) was 292. The present invention, in contrast, is based on practically the whole Finnish population (nearly 5 million people). The average prevalence of type 1 diabetes in children vaccinated with OPV was 272/100,000 by the age of 8 years, whereas the average prevalence in children receiving IPV instead of OPV was 326/100,000 by the age of 8 years. This difference in prevalence of type 1 diabetes

between the cohort receiving OPV, and the cohort receiving only IPV was significant ($p<0.01$ in student's t-test). These experiments are described in the paragraph bridging pages 14 and 15, and in Figure 1 of the specification. Applicants thus respectfully submit specification clearly shows that the that OPV has a preventive effect on the development of type 1 diabetes.

In this connection Applicants also wish to draw the Examiner's attention to the last paragraph at page 4 of the Graves article, which reads "Increased or decreased diabetes risk resulting from vaccines may only affect certain children at particularly high genetic risk for the disease, if vaccines affect the risk at all." In other words the authors do not exclude the possibility of vaccines being effective against diabetes type 1.

The recent publication by **Viskari et al.** deals with the relationship between the incidence of type 1 diabetes and enterovirus infections, and the inverse correlation found between them. The explanation of the inverse correlation is that complications of enterovirus infections become more common in an environment with a decreased rate of infections. The present invention, however, focuses on the effect of OPV on type 1 diabetes, and the inventors have shown that OPV has a statistically relevant effect on the prevalence of IDDM, which is a fact that cannot be cast in doubt by the (few) articles that have not implied a relationship between enterovirus infection and type 1 diabetes.

Regarding the relationship between virus infection and type 1 diabetes, Applicants respectfully submit that the connection between enterovirus infections and type 1 diabetes has also been since shown in a number of studies carried out in different countries using different methods. The great majority of these studies indicate a clear risk effect. The progress in this area has been rapid during the past few years, and the development of new methods has led to the detection of the virus from the blood of diabetic patients by RT-PCT, and large scale prospective studies have confirmed the risk effect. In addition, recently the virus has been found in the insulin producing cells in the pancreas of diabetic patients in four independent studies. The inventors have been studying the role of enteroviruses in type 1 diabetes for 20 years, and found the risk effect unequivocally in several patient series. Particularly important have been their findings in prospective studies showing the virus at the time when the process starts, several years before clinical diabetes is diagnosed. Enterovirus infections cluster to this particular time period immediately preceding the first appearance of diabetes-associated autoantibodes in a child's circulation. These findings have been consistent and observed in several study series using different methods. This work has led to several publications in high-quality scientific journals.

In view of the above, Applicants respectfully submit that the USPTO has not set forth even a *prima facie* case of alleged lack of enablement that is sufficient to cast doubt on the accuracy of Applicants' presumptively accurate disclosure. In any event, it is respectfully submitted that, in view of the knowledge and experience that those of skill in the art have had in the administration of OPV for the treatment of polioviruses

and the disclosure in the specification that the same dosages can be used in the claimed administration, no more than routine (not undue) experimentation would be required to practice the invention as claimed.

Claims 2, 6, 20 and 22 have been rejected under 35 USC 102(b) as allegedly being anticipated by Harjulehto-Mervaala et al. Claims 2-4, 20, 23 and 24 have been rejected under 35 USC 102(b) as allegedly being anticipated by the WHO Weekly Epidemiological Record. Applicants respectfully traverse these rejections.

The Examiner has cited the aforementioned publications on the basis of alleged inherency: the Examiner considers that the methods described in each of the cited publications would inherently have prevented type 1 diabetes. However, to constitute an anticipation on the basis of inherency, the prior art reference must **necessarily** include all of the claim limitations; it is not sufficient that a certain result or characteristic **may** occur or be present in the prior art (see MPEP Section 2112(IV)).

The claims that have been rejected over the cited art have all been amended to limit the recited treatment regimen to subjects who are in high risk groups for contracting type 1 diabetes. The cited art does not show that OPV was **necessarily** administered to people in such groups. It *a fortiori* does not show or suggest a step of selecting people at higher risk of diabetes for administration of the OPV (see claim 36). Accordingly, it is respectfully submitted that the claims as amended are not

anticipated by the cited art, either inherently or otherwise.

In view of the above, it is respectfully submitted that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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